REMARKS

Claims 7 and 39-43 are pending in this application.

The Amendments

The amendments in Claims 7, 39-40 and 43 are supported, for example, by page 5, lines 16-20; page 7, line 14, to page 8, line 6; page 8, lines 29-34; page 11, lines 28-34; and page 37, line 32 to page 38 line 18. New Claim 44 is supported, for example, by page 5, lines 16-20 and page 7, line 14 to page 8, line 6.

No new matter is added in the amendments. The Examiner is respectfully requested to enter the amendments.

The Response

Objections to Disclosure

Claim 7 is objected to by the Examiner for reciting the language "unaffected individual." The Examiner states that such language allegedly fails to make clear what the individual is unaffected by. Applicant has amended the claim to remove the language "unaffected."

Claim 7 is also objected to because part of claim 1 is allegedly drawn to a non-elected invention, i.e. a method for diagnosing prostate cancer. Applicants believe that the Examiner has mistakenly referred to Claim 7 in the instant office action, and not Claim 1. As a result, Applicants respectfully point out that Claim 7 is explicitly drawn to a method of diagnosis of prostate or breast cancer, comprising determining the *expression level of a gene* encoding PAA3 protein, not to the determination of the PAA3 protein level expression. Because the language of Claim 7 is drawn a method of diagnosis using gene expression, and not protein expression, the objections to Claim 7 should be withdrawn.

35 U.S.C. §112 Second Paragraph Rejection

Claims 7 and 40-43 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter to which Applicant regards as his invention. This rejection is overcome in view of the amendments.

Applicants have amended Claim 7 to recite determining the expression of a gene

encoding SEQ ID NO: 2 and a prostate tissue sample.

Therefore, the §112, second paragraph rejection of Claims 7 and 40-43 should be withdrawn.

35 U.S.C. §112 First Paragraph Rejection, Enabling

Claims 7 and 40-43 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. The rejection to the claims is traversed in part and overcome in part in view of the amendments.

Applicants have amended Claims 7, 39, 40 and 43, and added new Claim 44 to recite determining the expression of a gene encoding SEQ ID NO: 2 (the amino acid sequence of PAA3) and a prostate tissue sample.

The Examiner contends that the method of in vitro transcribing cRNA's from cancer or normal tissues is not efficient, making the identification of expressed genes difficult with this system. In addition, the Examiner contends that enhancers present in *in vivo* transcription may not be present in *in vitro* transcription, affecting the transcription efficiency and making unpredictable the method of identifying over- or under-expressed genes in prostate cancer tissue as compared to normal tissue. Applicants respectfully disagree with the Examiner's contentions.

Firstly, Applicants have already demonstrated that the methods described in the instant application possess the sensitivity and specificity to identify tumor markers of prostate cancer with the working example disclosed therein. As seen in page 69 of the specification, Applicants performed extensive control reactions on at least 90 control samples made up of body tissues, including adrenal gland, aorta, aortic valve, bladder, bone marrow, brain, breast, colonic epithelium, etc. As compared to samples from 54 different primary prostate tumors, only prostate tissue showed increases in expression levels as compared to the normal tissues above. These results verify that the methods disclosed in U.S. Application Nos. 09/733,288 and 09/687,576, of which this application claims priority to, that the gene encoding PAA3 was overexpressed in prostate cancer tissue samples as compared to hundreds of other genes screened on the biochip array. Therefore, the methods disclosed in the instant application allow one of ordinary skill in the art to identify over or under expressed genes in prostate or breast cancer

patients.

Secondly, Applicants respectfully disagree with the Examiner that the methods disclosed in the instant application cannot be reliably used to identify tumor markers that are overexpressed in prostate cancer. The method of transcribing cRNA's for amplification and analysis of gene expression is well known to those of ordinary skill in the art, and is widely utilized as a means of determining expression levels of specific gene sequences. *See* Lockhart et al., "Expression Monitoring by hybridization to high density oligonucleotide arrays" Nature Biotechnology 14:1675-1680 (1996) (copy enclosed). As further support, the manufacturers for microarrays have long recommended this technique for gene expression analysis. *See* Affymetrix website at http://www.affymetrix.com/technology/ge_analysis/index.affx (copy enclosed). Therefore, those of ordinary skill in the art have readily used the technique disclosed in the specification for gene expression analysis for the discovery of many differentially expressed genes in different disease or treatment states.

Thirdly, the Examiner's citation of U.S. Patent No.6,271,002 to Linsley et al. does not support his contention that cRNA in vitro transcription and gene expression is inefficient. The '002 patent merely discloses that cRNA is inefficient because it does not amplify as readily as PCR, and therefore requires a larger sample of mRNA as compared to PCR assays. See column 3, lines 2-6. An assay is not rendered unreliable simply because more starting sample is needed to conduct the assay. The cRNA methods and expression assays disclosed in the instant specification are reliable given the large milligram amounts of starting material used in the disclosed assays. *See* page 61, lines 12-14.

Fourthly, Applicants disagree with the Examiner's contention that the presence or absence of enhancers may differentially affect the transcription efficiency, rendering the assay unreliable. As disclosed in the specification, T7 primers and T7 polymerase are used for transcription of cDNA. The cDNA was in turn reverse transcribed from mRNA. *See* Ambion article, "The Basics: In Vitro Transcription" at http://ambion.com/techlib/basics/transcription/index.html (copy enclosed) for details. T7 polymerase is very efficient, and requires no additional enhancer activity to achieve high transcription rates. It is for this reason that T7 polymerase is used in the instant system, to allow amplification of the mRNA transcript without compromising fidelity of the transcript. See

Linsley '002 patent, column 3, lines 2-6. Those of ordinary skill in the art have long used T7 polymerase in expression assays for efficient and faithful transcription of isolated mRNA. *See* articles cited above, as well as Ambion website for additional references. Moreover, the methods disclosed in Lewin (1983, Genes) and cited by the Examiner relate to RNA polymerase II mammalian promoter systems, a promoter that is far less efficient than the T7 phage promoter, and therefore which enhancers are more likely to effect.

The Examiner's contention that because the total original mRNA's represented by cRNA's were allegedly not disclosed in the specification, the results may not be accurate in the instant application. Applicants respectfully disagree with the Examiner and point out that as disclosed throughout the Examples section, quality control and quantification of starting RNA or cRNA was done at various stages of the assay. *See* page. 62, lines 9-14, page 66, line 5.. More importantly, however, marker genes were identified through their increased expression levels as compared to other hundreds of genes immobilized on the oligonucleotide hybridization microarray (see U.S. Application Nos. 09/733,288 and 09/687,576, for which the instant application claims priority to). Therefore, it is the relative expression of many genes within a given tissue sample as compared to normal tissue sample that is relevant.

The Examiner contends that there is allegedly no disclosure to show that the sequence disclosed in SEQ ID NO:1 is the same as accession number AA609723. Applicants respectfully disagree with this contention. As known by those of ordinary skill in the art, and as provided by U.S. Application Nos. 09/733,288 and 09/687,576, accession numbers are readily accessed through National Center for Biotechnology Information Genbank's website. *See* http://www.ncbi.nlm.nih.gov/Genbank/index.html. When querying Genbank for accession number AA609723, a 257 bp sequence is pulled from the database (copy of Genbank sequence enclosed). Thus, those of ordinary skill in the art, guided by the disclosure provided, would know where to find the sequence contained within Genbank Accession No. AA609723. Moreover, one of ordinary skill in the art, guided by the instant specification, could perform a comparison between the sequence disclosed in accession number AA609723 and the nucleic acid sequence disclosed in SEQ ID NO:1 and show that there is indeed complimentary identification between the sequence comprising SEQ ID NO:1 and the sequence disclosed in accession number AA609723.

Therefore, the assays described in the specification are reliable, and are supported by those of ordinary skill in the art.

35 U.S.C. §112 First Paragraph Rejection – Written Description

Claims 7 and 40-43 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not containing a written description of the invention in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. This rejection is overcome in view of the amendments and Applicant's remarks below.

Claims 7, 40-43 allegedly does not adequately describe the scope of the claimed genus. Claim 7 has been amended to remove the term "and fragment thereof" and recite determining the expression of a gene encoding an amino acid sequence of SEQ ID NO:2. Applicants have also amended Claim 40 to recite "a nucleic acid probe complementary to SEQ ID NO:1."

Therefore, the § 112 first paragraph rejection of Claims 7 and 40-43 should be withdrawn.

35 U.S.C. §112 First Paragraph Rejection, Scope

Claims 7 and 39-43 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not reasonably providing enablement for a method for detecting prostate cancer, and allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is overcome in view of the amendments and Applicant's remarks below.

Claims 7 and 43 have been amended to remove the term "and fragment thereof" now recites determining the expression of a gene encoding an amino acid sequence of SEQ ID NO:2, and wherein said normal prostate tissue is from said first individual. In addition, Claim 7 has been amended to specify that the sample for detecting expression of a gene encoding an amino acid sequence of SEQ ID NO:2 is from the prostate tissue obtained from a first individual.

Claims 7 and 43 are rejected by the Examiner as allegedly pertaining to unrelated polynucleotide sequences beyond the scope of the specification. Claims 7 and 43 have been amended to remove the term "and fragment thereof" and recite determining the expression of a gene encoding an amino acid sequence of SEQ ID NO:2, and wherein said normal prostate tissue

is from said first individual.

Claims 7 and 39-42 are rejected by the Examiner as allegedly pertaining to tissue other than prostate tissue, which is beyond the scope of the specification. Claim 7 has been amended to specify that the sample for detecting expression of a gene encoding an amino acid sequence of SEQ ID NO:2 is from the prostate tissue obtained from a first individual, and whereby the expression in said prostate tissue is compared to expression of said gene from normal prostate tissue.

Claims 7 and 39-43 are rejected by the Examiner as allegedly teaching outside of the scope of the specification regarding determining a difference in the expression of a gene encoding SEQ ID NO:2. Claim 7 has been amended to specify that a higher level of expression in the first prostate tissue sample indicates that the first individual has prostate cancer.

Claims 40-42 are rejected by the Examiner as allegedly encompassing any unrelated polynucleotide sequence as a nucleic acid probe, which may not necessarily be specific for SEQ ID NO:1. Claim 40 has been amended to specify that the nucleic acid probe measures the expression of the nucleic acid sequence disclosed in SEQ ID NO:1, and that the nucleic acid probe claimed is complementary to SEQ ID NO:1. One of ordinary skill in the art, therefore, would extrapolate that the nucleic acid sequence used in the method for detecting expression of the nucleic acid sequence disclosed in SEQ ID NO:1 must be specific for said SEQ ID NO:1 nucleic acid sequence, and not an unrelated polynucleotide sequence.

Therefore, the § 112 first paragraph rejection of Claims 7 and 39-43 should be withdrawn.

35 USC §102(e) Rejection

Claims 7 and 39-43 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Schlegel, *et al.* (PCT US 01/05171). The rejection to the claims is traversed in part and overcome in part in view of the amendments.

Claim 7 has been amended to remove the term "and fragment thereof" and recite determining the expression of a gene encoding an amino acid sequence of SEQ ID NO:2.

The Examiner alleges that Schlegel, *et al.* discloses human prostate expression marker cDNA 21958 from Library cMhqal (table 8). Applicants respectfully point out that said human

prostate expression marker was not included in the PCT application attached to the instant office action, and cannot be retrieved through the European Patent Office Database. Nevertheless, Applicants believe, as the Examiner contends, that said human prostate expression marker cDNA 21958 has some homology but is not identical to the gene encoding SEQ ID NO: 2. As the Examiner has pointed out at page 21 of the instant office action response, the gene sequence identified as cDNA 21958 in table 8 of the Schlegel PCT application is not identical to SEQ ID NO:1. In view of the Amendments above, and because the Schlegel gene sequence is not identical to the SEQ ID NO:1 of the instant application, one of ordinary skill in the art would to the contrary not expect that the method taught by PCT/US 01/05171 would detect the claimed sequence of SEQ ID NO:1. Instead, one of ordinary skill in the art, if following the methods of Schlegel, would expect to detect the sequence specifically disclosed in the Schlegel PCT application because one of ordinary skill in the art would assume that a practitioner of the disclosed invention would design a probe sequence specific to the sequence at interest. Avoiding detection of non-specific and non-applicable sequences is essential to the operation of detection assays. *See* Lockhart et al., Nature Biotechnology above. Therefore, the instant a falls outside of the claim and scope specification, and thus outside of the disclosed invention of Schlegel, *et al.*

Because Schlegel, *et al.* do not disclose a sequence encoding SEQ ID NO: 2, the §102(e) rejection of Claims 7 and 39-43 should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109.

Respectfully submitted,

Date: August 25, 2003

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